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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,520	07/14/2003	W.O. Richter	1328/2/2	8231

25297 7590 03/13/2006

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,520	RICHTER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are pending.

2. Applicant's election with traverse of Group IV, claims 15-15 drawn to an adsorber column comprising a matrix and a ligand, wherein the ligand has specificity for fibrin filed on 12/08/05, is acknowledged.

Applicant's traversal is on the grounds that claims 16-17 depend from claim 13 and thus a rejoinder is requested. Applicant further submits that claims 1-18 are directed at least in part to the removal of or the adsorption of fibrin and/or fibrinogen and could be viewed as linked by a single unifying concept. Finally, Applicant submit that it would not present an undue burden for the Patent Office to search and examine all of the pending claims at one time. This is not found persuasive because as stated in the previous office actions that Adsorber columns, peptides, and antibodies differ with respect to their structures and physicochemical properties; therefore each product is patentably distinct. In addition, the various method of treating differ with respect to ingredients (peptides and antibodies), method steps, and endpoints; therefore, each method is patentably distinct. Therefore the methods and the products are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-12 and 16-18 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 13-15 are under examination as they read on an adsorber column comprising a matrix and a ligand, wherein the ligand has specificity for fibrin and/or firbrinogen.

5. The specification on page 1 should be amended to reflect the status of parent application No. 09/462,446.

6. The specification is objected to under 37 CFR 1.821(d) because the SEQ ID NOS are not disclosed in the specification adjacent referenced sequences (for example, sequences appear on pages 7, 8, and 10 of the instant specification that appear to correspond to SEQ ID NOS:1-8, but that lack identifiers). Appropriate correction is required.

7. Applicant's IDS, filed 12/08/05, is acknowledged. The references cited in the Search Report of PCT/EP 98/04090 have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed within the set period for reply to this Office Action.

8. Claim 14 is objected to under 37CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claims.

9. Claims 13-15 are objected to for the following informalities: the article "an" should inserted before "Adsorber column" in claim 13, and the word "The" should be inserted before "Adsorber coloumn" in claims 14-15. correction is required.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 15 contains the trademark/trade name Sepharose. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe beads and, accordingly, the identification/description is indefinite.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adsorber column containing a matrix and a peptide, wherein the peptide consists of SEQ ID NO: 1 or 2, does not reasonably provide **enablement** for any adsorber column containing a matrix and "any ligand", wherein said ligand has a specificity for fibrin and/or fibrinogen in claim 13, wherein the ligand is a peptide "containing the amino acid sequence: Gly-Pro-Arg-Pro-x, wherein x can be any desired amino acid or spacer, or wherein the ligand is a peptide "having" the amino acid sequence Gly-Pro-Arg-Pro-Lys in claim 14, whereinthe matrix is Sepharose in claim 15 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Applicant has not provided sufficient biochemical information that distinctly identifies such "ligand" other than SEQ ID NOS: 1 and 2. It is recognized in the art that ligands must posses significant structural and chemical complementarity to their target receptors (Kuntz, Science, 1992, Vol. 257:1078-1082, especially page 10709, 2nd col., lines 1-4 and 9-12 under heading "Structure-Based Design) and that ligands generally bind to native states of proteins with little or no interaction with unfolded states (Miller et al, Protein Science, 1997, 6:2166-2179, especially page 2166, 2nd col., lines 18-20) and further that alterations in protein structure lead to alterations in bindings affinity proportional to the magnitude of the alteration (Miller et al, abstract, lines 2-4). Finally, Kuntz teaches that as little as 2% of compounds predicted to inhibit specific enzymztic or receptor systems actually shown inhibition in the micromolar range (page 1080, 3rd col.).

Further, claim 14 recites that the liagand is a peptide "containing" or "having" SEQ ID NO: 1 or 2. However, the terms "conatining" and "having" are open-ended, they expand the peptide's sequence of SEQ ID NOS: 1 and 2 to include additional amino acids at either or both N-terminal or C-terminal. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies peptides other than those encompassed by SEQ ID NO: 1 and 2. There is insufficient direction or objective evidence as to how to make and to how to use any peptide which has a specificity for fibrin and/or fibrinogen for the number of possibilities associated with the myriad of direct and indirect effects associated with various peptide and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of any "agent" and still provide or maintain the claimed adsorption activities is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Hau *et al* (Biochem Biophys Res Commun. 1996 May 15;222(2):576-83).

Hua *et al* teach the CH-Sepharose Gly-Pro-Arg -H adsorber column containing a matrix (Sepharose) and a ligand (Gly-Pro-Arg), wherein the Gly-Pro-Arg ligand has a specificity for fibrin and/or fibrinogen (see page 577, under *Protein purification* in particular).

Further, Hua *et al* teach that using said method was able to purify renaturated GPRP-u-PA protein to homogeneity by one step CH-Sepharose 4B-Pro-Gly-Arg-H affinity chromatograph (see page 578, 1st full paragraph in particular). Hua et al teach that short peptide beginning with the sequence glycyl-Lprolyl-L-arginin (Gly-Pro-Ar) which corresponds to the amino-terminal segment of the fibrin α chain after the release of the fibrinopeptide A, can prevent the polymerization of fibrin monomers. Further these peptides bind to fibrinogen and the plasmin-generated fragment D. Although Gly-Pro-Arg itself was found to be effective inhibitor of polymerization, the addition of a fourth residue, particularly proline or sarcosine, significantly increased both the binding and the inhibitory activity (see page 576, last paragraph in particular).

The reference teachings anticipate the claimed invention.

16. Claims 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuyas (a) *et al* (IDS ref. NO. 2).

Kuyas *et al* teach the Gly-Pro-Arg-Pro-Lys-Fractogel adsorber column containing a matrix (Fractogel) and a ligand (Gly-Pro-Arg-Pro-Lys), wherein the Gly-Pro-Arg-Pro-Lys ligand has a specificity for fibrin and/or fibrinogen (see abstract and page 440, col., 1 paragraphs 2-4 in particular).

The reference teachings anticipate the claimed invention.

17. Claims 13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuyas (b) *et al* (Thrombosis and Haemostasis, 1995, vol. 54, No. 1, pp. 40-40).

Kuyas et al (1995) teach an adsorber column containing Gly-Pro-Arg-Pro-Sepharose, wherein the Gly-Pro-Arg-Pro (GPRP) is the ligand and Sepharose is the matrix (see the entire abstract). Kuyas et al teaches GPRP-Sepharose affinity chromatograpy is a fast and reproducible method and ideal for the isolation of fibrinogen from small a mounts of plasma. It is superior to any available method for the isolation of abnormal fibrinogens provided the c-terminal binding site is intact (see the entire abstract).

The reference teachings anticipate the claimed invention.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being obvious over Kuyase (1990a) *et al* in view of Kuyas (1995b) *et al.*

The teachings of Kuyas (a) *et al* reference have been discussed, supra. Kuyas (1990a) *et al* further teaches that human fibrinogen has a strong affinity for fibrin. Therefore, fibrin immobilized on Sepharose is used to isolate fibrinogen from human plasma by affinity chromatography. Kuyas *et al* further teach that the terapeptide GlyProArgPro, containing the N-terminal sequence of the α-chain of fibrin being exposed upon the action of thrombin on fibrinogen, competitively inhibits the fibrin polymerization. It also binds to fibrinogen. In addition the N-terminal amino acid sequence GlyProArg is involved in the inhibition of the fibrin polymeriazation by binding to the complementary binding site of an other fibrin(ogen) molecule (see *Introduction* on page 439 in particular). Lastly Kuyas et al teach that the addition of a second proline enhances the affinity of the peptide Gly ProArgPro for fibrinogen almost tenfold. Further, to have the peptide distant enough form the gel matrix a further amino acid, lysine, was included in the peptide as a spacer (see page 443, 1st col., last full paragraph in particular).

The claimed invention differs from the Kuyase (a) *et al* reference teachings only by the recitation that the matrix is Sepharose in claim 15.

However, Kuyas et al (1995b) teach an adsorber column containing Gly-Pro-Arg-Pro-Sepharose, wherein the Gly-Pro-Arg-Pro (GPRP) is the ligand and Sepharose is the matrix (see the entire abstract). Kuyas et al teaches GPRP-Sepharose affinity chromatograpy is a fast and reproducible method and ideal for the isolation of fibrinogen from small a mounts of plasma. It is superior to any available method for the isolation of abnormal fibrinogens provided the c-terminal binding site is intact (see the entire abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the peptide GlyProArgPro taught by Kuyas (1995b) et al with the pentapetide GlyProArgProLys taught by Kuyas (1990a) *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so to have the peptide distant enough form the gel matrix a further amino acid, lysine, is included in the peptide as a spacer as taught by Kuyas (1990a) *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 6, 2006

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